REMARKS / ARGUMENTS

Claims 1-19 are replaced by new claims 20-39. Applicant believes that no additional fees for are due for the new claims.

The new claims are supported the original claims and by the specification, for example, the paragraph bridging pages 32 and 33, the first paragraph on page 34, page 36, and page 38, fifth paragraph.

Claims 9 and 14-16 were rejected under 35 USC 112, second paragraph. Applicant believes that the new claims do not include any of the items pointed out by the Examiner as the basis for the rejection. Accordingly, withdrawal of the rejection is requested.

Claims 3, 8-9, and 14-16 were rejected under 35 USC 101 and under 35 USC 112, second paragraph. Applicant believes that the new claims do not include the stated basis for the rejections. Accordingly, the Examiner is requested to withdraw these rejections.

Claims 3, 8-9 and 13-16 were rejected under 35 USC 112, first paragraph. The claims here presented do not recite "curative, palative or prophylactic treatment." Accordingly, Applicant believes that the new claims should not be subject to this rejection.

Claims 3, 8 and 11 were rejected under 35 USC 103(a) over Longley et al in view of Goekjian et al. Applicant requests reconsideration and withdrawal of this rejection for the reasons that follow.

Applicant believes that present claim 20 corresponds to the claims included in this rejection and will address the patentability of claim 20 over the Longley et al and Goekjian et al references.

Longley et al is relied on as disclosing that the consistent finding of activating c-kit mutations in mast cell tumors together with the ability of activated kit to stimulate mast cell proliferation and transformation suggests that these mutations are necessary, if not sufficient for

some forms of mastocytosis. Longley et al is further relied on as teaching that inhibiting the activating mutant kit with kit inhibitors might provide symptom relief, decrease mast cell load and might eventually provide a cure. Applicants assert that such a disclosure merely provides a theoretical basis to experiment with kit inhibitors for the treatment of mastocytosis. However, since it is clearly speculative, it does not provide a reasonable expectation that the experiments would be successful. Moreover, it does not suggest that PKC412 would be an inhibitor of such an activating mutant kit.

Longley et al is additionally relied on as demonstrating that kit kinase inhibitors can effectively kill neoplastic mast cells which cause some forms of mastocytosis. However, the experiments discussed in the reference showed that kit inhibitors have variable activity against the activating mutations included in the experiment. Such a teaching would merely lead the skilled artisan to try to find kit inhibitors that target the appropriate activated mutant kit and to conduct further experiments with such kit kinase inhibitors.

The reference discloses that canine c-kit contains a point mutation resulting in substitution of tyr for Asp814, the equivalent position of human Asp816, which causes constitutive receptor activation in most cases of adult mastocytosis. This disclosure suggests a potential drug target that is associated with human mastocytosis: human kit kinase with a point mutation resulting in substitution of tyr for Asp816, also known as the D816V kit mutation.

However, and significantly, at pages 692-693, Longley et al discloses that the known kit inhibitors used in the experiment had variable activity against P-815 c-kit. Of the five indolinone kit inhibitors tested, only one, SU6577, at a concentration of 40 μM, could substantially reduce constitutive kit phosphorylation in the canine P-815 cell line. The caption under Figure 2 discloses that only SU4984 and SU6577 kill P-815 cells. At page 693 and at the Summary on page 694, the reference further discusses the variable activity against the activating mutations included in the experiment.

In view of the results of these experiments and Longley et al's discussion of them, it is clear that the reference does not provide a general teaching that kit kinase inhibitors can effectively kill neoplastic mast cells. Instead, it teaches that kit inhibitors have variable activity against the different activating kit mutations and that a kit kinase inhibitor must inhibit the specific mutant form of kit kinase to be effective. Such a teaching clearly does not lead the skilled artisan to generally expect inhibitors of wild-type kit to provide a therapeutic benefit

against a condition associated a mutant form of kit kinase. Instead, with respect to human mastocytosis, it would lead the skilled artisan to want to identify inhibitors of the D816V mutant kit, and to conduct further experiments with them.

Goekjian et al is relied upon as disclosing that PKC412 is a non-toxic kit inhibitor. However, Goekjian et al is not even alleged to disclose anything about the ability of PKC412 to inhibit kit with the D816V mutation, the mutation which Longley et al discloses as the cause of constitutive receptor activation in most cases of adult mastocytosis. Therefore, Goekjian et al does not supply a teaching that overcomes the deficiencies of the primary reference.

For the reasons discussed above, Applicant asserts that Longley et al, at best, would lead the skilled artisan to try to find kit inhibitors that target the activated mutant kit which is believed to cause the mastocytosis, specifically the D816V mutation. Since Goekjian et al does not provide any basis for the skilled artisan to expect PKC412 to have activity against any particular activated mutant kit, or more particularly an activated mutant kit associated with mastocytosis, the combined disclosure of the references would not lead the skilled artisan to have any expectation with respect to PKC412's potential for treating mastocytosis. Therefore, the invention of claim 20 and its dependent claims are patentable over the combined disclosure of Longley et al and Goekjian et al.

The Examiner's attention is directed to the three articles from Blood which are enclosed: Growney et al, Blood, **106(2)**, 721-724 (2005); Gotlib et al, Blood, **106(8)**, 2865-2870 (2005), Gleixner et al, Blood, **107(2)**, 752-759 (2006). None of these articles are prior art to this application. However, the discussion in these publications supports the patentability of the present claims.

The Growney et al article describes experiments wherein PKC412 is tested against a panel of kit mutations, including D816V/Y mutations that are associated with systemic mast cell disease (SMCD in the publication), gastrointestinal stromal tumors (GIST) and acute myeloid leukemia (AML). These experiments demonstrate that PKC412 is almost 250 times more active against the D816V kit mutant than another kit inhibitor, imatinib. See, Table 1. IC_{50} =10651 nM (imatinib) vs. 44 nM (PKC412). Nothing in the references would lead the skilled artisan to expect PKC412 to be so much more potent against this particular kit mutation. In addition, the results confirm that both of the kit inhibitors have variable activity against the other mutated forms of kit kinase included in the experiments.

The Gottlib et al article describes the response of a patient suffering from several conditions, including systemic mastocytosis, and concludes that PKC412 has promise in the treatment of aggressive forms of systemic mastocytosis.

The Gleixner et al article describes experiments comparing the D816V mutant kit inhibiting ability of PKC412 and another kit inhibitor, AMN107, which is now an approved drug marketed under the brand Tasigna. The article indicates that PKC412 is a more potent inhibitor of D816V mutant kit. PKC412 also inhibited growth in 2 subclones of HMC-1 that either expressed or lacked the D816V mutant kit and concludes that PKC412 seems to be the first tyrosine kinase inhibitor that counteracts growth of KIT D816V bearing human MCs in the same way as MCs expressing wild type kit. The article further reports that the growth-inhibitory effects of PKC412 on neoplastic MCs are associated with both inhibition of mutated kit and with apoptosis. Nothing in the relied upon references would lead the skilled artisan to expect PKC412 to possess such properties. The article concludes that PKC412 seems to be a novel attractive targeted drug worthy to be considered for use in clinical trials in ASM or MCL. See, page 755 right column, first paragraph and the discussion section on pages 757-758.

For the reasons discussed above, Applicant requests withdrawal of the rejection of claim 20 and its dependent claims over Longley et al in view of Goekjian et al.

Claims 9 and 12 were rejected under 35 USC 103(a) over Longley et al in view of Goekjian et al in further view of Ma et al. Applicant requests reconsideration and withdrawal of this rejection for the reasons that follow.

Applicant believes that present claim 30 most closely corresponds to the claims included in this rejection because it relates to a method of treating imatinib resistant mastocytosis with the compound for formula (VII) (hereinafter referred to as PKC412). Therefore, in response to this rejection, Applicant will primarily address the patentability of claim 30 over the cited references.

As the examiner recognizes, Longley et al and Goekjian et al do not teach treatment of mastocytosis resistant to imatinib.

Ma et al is relied upon as teaching that certain types of mastocytosis are characterized by mutation in c-kit position 816 causing constitutive activation of the Kit kinase and as teaching that certain mastocytosis is resistant to imatinib. Such a disclosure, at best, describes the problem solved by the present invention – to discover a therapeutic agent that inhibits the kit kinases which cause mastocytosis when another kit kinase inhibitor, imatinib, does not. However, it does not provide any information that would lead the skilled artisan to have a reasonable expectation that PKC412 would be useful where imatinib fails. Therefore, combined disclosure of the references does not provide the skilled artisan a basis to have a reasonable expectation that PKC412 would be useful for the treatment of mastocytosis that is resistant to imatinib.

Claims 13-16 were rejected under 35 USC 103(a) over Longley et al in view of Goekjian et al in further view of Ma et al in further view of Caravatti et al. Applicants request reconsideration and withdrawal of this rejection for the same reasons that are discussed above with respect to the other rejections under 35 USC 103(a).

Entry of this amendment and reconsideration and allowance of the claims are respectfully requested.

Respectfully submitted,

George R. Dohmann
Attorney for Applicant
Reg. No. 33,593

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Building 104
East Hanover, NJ 07936-1080
(862) 778-7824

Date: August 6, 2009

Enc.: Blood 2005 106:2865-2870
Blood 2005 106:721-724
Blood 2006 107:752-759